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EXAMINER	
OUSPENSKI, ILIA I	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/955,866	FOX ET AL.	
	Examiner	Art Unit	
	ILIA OUSPENSKI	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-58* is/are pending in the application.

4a) Of the above claim(s) *9,12-42 and 46-56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8, 10, 11, 43-45, 57, and 58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The examiner of this application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Ilia Ouspenski, Group Art Unit 1644, Technology Center 1600.

Claims 1 – 58 are pending.

2. Applicant's response to Restriction Requirement, filed on 03/04/2004, is acknowledged. Applicant's election of invention of Group I,

Claims 1 – 8, 10, 11, 43 – 45, 57, and 58, drawn to an isolated nucleic acid comprising SEQ ID NO:1 and variants thereof; vectors, host cells, and methods of producing the polypeptide, is acknowledged.

Claims 9, 12 – 42, and 46 – 56 (non-elected groups II – XII) are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1 – 8, 10, 11, 43 – 45, 57, and 58 are under consideration in the instant application.

3. Sequence compliance: The instant application appears to be in sequence compliance for patent applications containing nucleotide sequence and/or amino acid sequence disclosures.

4. Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged.

5. Applicant's IDS, filed 01/16/2003, is acknowledged. Applicant is required to provide the *dates* for Other Documents – Non Patent Literature Documents. *All references should be dated and have page numbers.*

Applicant's submission of an International Search Report for PCT/US01/29183 on the IDS is acknowledged, however this citation has been crossed out as it is not appropriate for printing.

6. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention *to which the claims are directed.*

7. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code at least on page 82, line 11. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Applicant is requested to review the application for embedded hyperlinks and/or other forms of browser-executable code and delete them. Embedded hyperlinks and/or other form of browser-executable code are impermissible in the text of the application as they represent an improper incorporation by reference. See MPEP § 608.01 and 608.01(p).

The use of the trademarks, for example pGEM-T-Easy® (page 83, line 6), has been noted in this application. Each letter of the trademarks should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1 – 8, 10, 11, 43 – 45, 57, and 58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(A) Claims 1 – 3, and dependent claims thereof, are indefinite in the recitation of "at least moderately stringent conditions" in 1(d), 2(e), and 3(g). Although the specification discloses on pages 18 – 19 general parameters for calculating such conditions, in the absence of a clear definition of the metes and bounds of this phrase it is unclear which conditions are actually claimed.

It is suggested that Applicant amend claims 1 - 3 to recite a particular set of hybridization and wash conditions to overcome this rejection.

(B) Claims 2 and 3, and dependent claims thereof, are indefinite in the recitation of "activity of the polypeptide", in 2(a), 2(c), and 3(a) – 3(e), because it is unclear what activity is contemplated. Recitation of specific activities of PD-1 binding and inhibition of anti-CD3 mediated T-cell proliferation would be remedial in overcoming this rejection.

(C) Claim 2 and dependent claims thereof are indefinite in the recitation of "...***or*** the nucleotide sequence of DNA insert" in 2(a), because it is unclear whether the "at least about 70 percent identical" sequence is intended to modify the second "nucleotide sequence of DNA insert." In addition, the claim is indefinite because it is unclear whether the recitation "wherein the encoded polypeptide" is intended to modify the phrase before or after the "***or***."

(D) Claim 11 contains trademark/trade names GAP, BLASTN, FASTA, BLASTA, BLASTX, and BestFit. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See Ex parte Simpson, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe computer programs and, accordingly, the identification/description is indefinite.

(E) Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: claim 58 is indefinite in lacking proper antecedent basis in the specification. The claimed limitation of "array of nucleic acid molecules" is not adequately supported by the description of "microarrays" on pages 51 – 52 of the specification.

12. Claims 1, 2, 4 - 8, 10, 11, 43 – 45, 57, and 58 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is apparent that the "DNA insert in ATCC Deposit No. PTA 2481" is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 U.S.C. 112, first paragraph, may be satisfied by a deposit of the pertinent materials. See 37 CFR 1.801-1.809.

In addition to the conditions under the Budapest Treaty, Applicant is required to assure that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications (see 37 CFR 1.808 (a)(2) and MPEP 2410-2410.01).

Although applicant has deposited the "cDNA encoding human B7-L polypeptide, subcloned into pGEM-T-Easy" with the ATCC (page 81, lines 28 – 31), there appears to be no assurances indicated above. Applicant's provision of these assurances would obviate this rejection.

13. Claims 1 - 8, 10, 11, 43 – 45, 57, and 58 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated nucleic acid molecule comprising the nucleotide sequence as set forth in SEQ ID NO:1, the nucleotide sequence of DNA insert in ATCC deposit No. PTA 2481, and a nucleotide sequence encoding the polypeptide as set forth in SEQ ID NO:2 (claim 1(a) – 1(c)), does not reasonably provide enablement for a nucleotide sequence which:

hybridizes under at least moderately stringent conditions, or is complementary to B7-L, its variants or fragments (1d, 2e, 2f, 3g, 3h);
encodes an allelic variant or splice variant of B7-L (2b), or a polypeptide at least about 70 percent identical to the B7-L, which has an activity of B7-L (2a);
is a region of B7-L encoding a polypeptide of at least about 25 amino acids residues, which has an activity of B7-L, or is antigenic (2c);
is a region of B7-L or its variant of at least about 16 nucleotides (2d and 3f);
encodes a polypeptide with at least one amino acid substitution, deletion, insertion or truncation (3a – 3e).

The specification does not provide a sufficient enabling description of the claimed invention.

The specification discloses only a single nucleic acid sequence (SEQ ID NO:1, and DNA insert in ATCC Deposit No. PTA 2481, which are presumed to be identical) encoding a single polypeptide B7-L (SEQ ID NO:2) with a disclosed activity of binding to the PD-1 receptor (page 90) and inhibiting anti-CD3 mediated T-cell proliferation (page 91). The instant claims encompass in their breadth *any* nucleic acid encoding a polypeptide with at least 70% identity to B7-L, or *any* variant of the polypeptide, or *any* nucleic acid that hybridizes to SEQ ID NO:1, including those that comprise a region or a fragment thereof.

The claims recite:

(A) nucleotide sequences encoding "percent identity variants" of a B7-L polypeptide;

(B) nucleotide sequences that hybridize under at least moderately stringent conditions;

(C) allelic variants or splice variants;

(D) modifications of the nucleotide sequence, which result in amino acid substitutions, deletions, insertions, and/or truncations;

(E) subsequences and complementary sequences.

(A) "percent identity"

The claims recite a genus of nucleotide sequences encoding polypeptides having at least about 70% identity to a reference sequence, but do not require that the encoded polypeptides share any testable functional activity, a feature deemed essential to the instant invention. Applicant has disclosed one nucleic acid encoding the B7-L polypeptide, and thus has disclosed only one "variant". In the absence of a particular testable function and some structural basis for that function that must be maintained by the members of the genus, the claimed invention is not described in such a way as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention.

Attwood (Science 2000; 290:471-473) teaches that "[i]t is presumptuous to make functional assignments merely on the basis of some degree of similarity between sequences. Similarly, Skolnick et al. (Trends in Biotech. 2000; 18(1):34-39) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2).

Finally, even single amino acid differences can result in drastically altered functions between two costimulatory proteins. For example, Metzler et al. (Nature Structural Biol. 1997; 4:527-531) show that any of a variety of single amino acid changes can alter or abolish the ability of CTLA4 to interact with its ligands CD80 and CD86 (e.g., summarized in Table 2). Thus it is unpredictable if any functional activity will be shared by two polypeptides having less than 100% identity over the full length of their sequences.

In view of this unpredictability, the skilled artisan would not reasonably expect a polypeptide having anything less than *100% identity* over *the full length* of SEQ ID NO:2 to share the same function as the polypeptide of SEQ ID NO:2. The limitation of "having an activity of the polypeptide set forth in SEQ ID NO: 2" is not seen as providing a requisite functional activity for the nucleic acid encoding the polypeptide both because, as noted supra, the term is ambiguous; and because even if the polypeptide is limited in binding to the PD-1 receptor or inhibiting anti-CD3 mediated T-cell proliferation, there is insufficient guidance to direct the skilled artisan as to those essential sequences for the disclosed activities.

Neither is the term "antigenic" (claim 2(c)) seen as sufficiently limiting since antigenic peptides may be as small as 6-15 shared amino acid residues (e.g., Lerner: Nature 1982; 299:592-596, see page 595-596) and places insufficient limitations on the function of the protein containing the polypeptide sequence.

Thus the recitation of percent identity language and limitations regarding the *sequence length* over which the percent identity is required, does not allow the skilled artisan to make and use the encoding nucleic acids commensurate in scope with the instant claims without undue experimentation.

(B) "hybridization"

Similarly, the fact that two nucleic acid sequences will hybridize under at least moderately stringent conditions (claims 1(d), 2(e), and 3(g)) does not in and of itself require that the two sequences share any functional activity. Thus the same observations apply to the recitation of "a nucleic acid that hybridizes under moderately stringent hybridization conditions" as were noted above with respect to "percent identity" language. Further, it was well known in the art at the time the invention was made that hybridization could occur between two sequence based upon short stretches of 100% identity. Thus a great deal of sequence variability *with respect to the full-length nucleic acid* is possible. Finally, hybridization under conditions other than high stringency would be expected to permit a great deal of variation between the two hybridizing sequences, making it even more unpredictable that the two sequences would share the same function.

Thus as for the recitation of percent identity, hybridization language and limitations regarding both the *hybridization conditions* and the *sequence length* over which the hybridization takes place; does not allow the skilled artisan to make and use the hybridizing nucleic acids commensurate in scope with the instant claims without undue experimentation.

(C) "allelic variants or splice variants"

The term "allelic variants" encompasses "one of several possible naturally occurring alternate forms of a gene occupying a given locus on a chromosome of an organism or a population of organisms," as disclosed in the specification as-filed on page10, lines 20 – 23. Similarly, a "splice variant" is a reference to "a nucleic acid molecule, usually RNA, which is generated by alternative processing of intron sequences in an RNA transcript of B7-L polypeptide" (page 10 lines 23 – 26). Applicant has not provided sufficient biochemical information (e.g. nucleic acid sequences, etc.) that distinctly identifies the *allelic variants or splice variants* of SEQ ID NO:1, (claim 2(b)), other than those set forth in SEQ ID NO:1 and ATCC Deposit No. PTA 2481.

It is not sufficient to define a specificity by its principal biological activity or structure, e.g. for allelic variants or splice variants of SEQ ID NO:2, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property. The specification appears to provide insufficient data on the existence of allelic variants or splice variants of SEQ ID NO:2.

Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use of the claimed protein in manner reasonably correlated with the scope of the claims broadly including any number of allelic variants or splice variants of SEQ ID NO:2. The scope of the claims must bear a reasonable correlation with the scope of enablement. The specification does not provide for sufficient enablement for allelic variants or splice variants of SEQ ID NO:2 other than that defined by SEQ ID NO:2.

(D) "modifications"

The instant claim language encompasses modifications of SEQ ID NO:2, such as amino acid substitutions, deletions, and insertions (claim 3). Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, Burgess et al (J Cell Biol. 111:2129-2138, 1990) show that a conservative replacement of a single "lysine" reside at position 118 of acidic fibroblast growth factor by "glutamic acid" led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. Similarly, Lazar et al. (Mol Cell Biol. 8:1247-1252, 1988) teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagines did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. Also, as noted supra, Metzler et al. (Nature Structural Biol. 1997; 4:527-531) show that any of a variety of single amino acid changes can alter or abolish the ability of CTLA4 to interact with its ligands CD80 and CD86 (e.g., summarized in Table 2). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein.

Furthermore, the specification fails to teach what deletions, truncations, substitutions and mutations of the disclosed sequence can be tolerated that will allow the protein to function as claimed. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with reasonable expectation of success are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or no substitutions. Residues that are directly involved in protein functions such as binding will certainly be among the most conserved (Bowie et al. Science, 247:1306-1310, 1990, p 1306, col. 2).

Thus the recitation of a range of possible protein sequence modifications, in the absence of guidance as to the specific nature of modifications resulting in a functional polypeptide, does not allow the skilled artisan to make and use the nucleic acids encoding the variant polypeptides commensurate in scope with the instant claims without undue experimentation.

(E) subsequences and complementary sequences.

The instant claim language appears to encompass subsequences. For example, claim 1(d) recites an isolated nucleic acid molecule that hybridizes to the complement of SEQ ID NO:1. Even under high stringency conditions, molecules shorter than the specified sequence are expected to meet this limitation. Further, claims 2(c) – 2(f) and 3(d) – 3(H) specifically read on regions, fragments, and truncations of SEQ ID NO:1.

However, the specification does not appear to have provided sufficient guidance as to which subsequences of SEQ ID NO:2 would share the activity of binding to PD-1 or inhibiting anti-CD3 mediated T-cell proliferation. Neither does the specification appear to have provided any working examples of any functional subsequences. Thus it would require undue experimentation of the skilled artisan to determine which subsequences of SEQ ID NO:2 would have the function of the full length molecule, and in turn identify nucleic acid subsequences of SEQ ID NO:1 or the nucleotide sequence of DNA insert in ATCC deposit No. PTA 2481 which encode these subsequences.

The recitation of "a nucleotide sequence complementary to the nucleotide sequence" in claims 1(e), 2(f), and 3(h) without further limitation that the complementarity is over the full length of the sequence, reads on subsequences and is subject to rejection on the grounds specified above.

The term "comprising" in claims 1 – 3 is open ended and extends the nucleic acid molecule to include additional non-disclosed sequences on either or both sides of the disclosed region. As the term "comprising" is applied to sequences other than full length B7-L sequences, such as regions, fragments, of hybridizing or complementary nucleic acid molecules, there does not appear to be sufficient guidance in the specification as filed as to how the skilled artisan would make and use the various nucleic acids recited in the instant claims. A person of skill in the art would not know which sequences are essential, which sequences are non-essential, and what particular sequence lengths identify essential sequences. There is insufficient guidance to direct a person of skill in the art to select particular sequences or sequence lengths as essential for binding to PD-1 or inhibiting anti-CD3 mediated T-cell proliferation. Without detailed direction as to which nucleic acid sequences are essential to the function of the encoded polypeptide, a person of skill in the art would not be able to determine without undue experimentation which of the plethora of nucleic acid sequences encompassed by the instant claims would share the ability to bind to PD-1 or inhibit anti-CD3 mediated T-cell proliferation of the encoded polypeptide of SEQ ID NO:2, other than the nucleic acid of SEQ ID NO:1 the nucleotide sequence of DNA insert in ATCC deposit No. PTA 2481, and a nucleotide sequence encoding the polypeptide as set forth in SEQ ID NO:2.

To summarize, reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary, the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

As noted supra, the skilled artisan would not reasonably expect a polypeptide having anything less than *100% identity* over *the full length* of SEQ ID NO:2 to share the same function as B7-L. The limitation of "having an activity" is not seen as providing a requisite enablement, because even if the activity is specified as binding to the PD-1 receptor and/or inhibiting anti-CD3 mediated T-cell proliferation, the specific sequences necessary for these properties are still unknown. Thus the teachings set forth in the specification provide no more than a plan or invitation for those skilled in the art to experiment practicing the claimed invention.

Limiting the scope of the claims in this Application to that of claims 1(a) – 1(c) would obviate this rejection.

14. Claims 1 – 8, 10, 11, 43 – 45, 57, and 58 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The following *written description* rejection is set forth herein.

Applicant is in possession of nucleic acid molecule of SEQ ID NO:1, the nucleotide sequence of DNA insert in ATCC deposit No. PTA 2481, and a nucleotide sequence encoding the polypeptide as set forth in SEQ ID NO:2.

Applicant is NOT in possession of any isolated nucleic acid molecule which:
hybridizes under at least moderately stringent conditions, or is complementary to B7-L, its variants or fragments (1d, 2e, 2f, 3g, 3h);
encodes an allelic variant or splice variant of B7-L (2b), or a polypeptide at least about 70 percent identical to the B7-L, which has an activity of B7-L (2a);
is a region of B7-L encoding a polypeptide of at least about 25 amino acids residues, which has an activity of B7-L, or is antigenic (2c);

is a region of B7-L or its variant of at least about 16 nucleotides (2d and 3f); encodes a polypeptide with at least one amino acid substitution, deletion, insertion or truncation (3a – 3e)

The specification does not describe the claimed subject matter in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification discloses only a single nucleic acid sequence (SEQ ID NO:1, and DNA insert in ATCC Deposit No. PTA 2481, which are presumed to be identical) encoding a single polypeptide B7-L (SEQ ID NO:2) with a disclosed activity of binding to the PD-1 receptor (page 90) and inhibiting anti-CD3 mediated T-cell proliferation (page 91). The instant claims encompass in their breadth *any* nucleic acid encoding a polypeptide with at least 70% identity to B7-L, or *any* variant of the polypeptide, or *any* nucleic acid that hybridizes to SEQ ID NO:1, including those that comprise a region or a fragment thereof.

The claims recite:

(A) nucleotide sequences encoding "percent identity variants" of a B7-L polypeptide;

(B) nucleotide sequences that hybridize under at least moderately stringent conditions;

(C) allelic variants or splice variants;

(D) modifications of the nucleotide sequence, which result in amino acid substitutions, deletions, insertions, and/or truncations;

(E) regions of nucleotide sequence encoding polypeptide fragment, and sequences complementary to a claimed sequence.

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 3rd column).

Regarding the instant claim limitations, the specification does not appear to provide an adequate written description for the following reasons:

(A) "percent identity"

The claims recite a genus of nucleotide sequences encoding polypeptides having at least about 70% identity to a reference sequence, but do not require that the encoded polypeptides share any testable functional activity, a feature deemed essential to the instant invention. Applicant has disclosed one nucleic acid encoding the B7-L polypeptide, and thus has disclosed only one "variant". In the absence of a particular testable function and some structural basis for that function that must be maintained by the members of the genus, the claimed invention is not described in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Attwood (Science 2000; 290:471-473) teaches that "[i]t is presumptuous to make functional assignments merely on the basis of some degree of similarity between sequences. Similarly, Skolnick et al. (Trends in Biotech. 2000; 18(1):34-39) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2).

Finally, even single amino acid differences can result in drastically altered functions between two costimulatory proteins. For example, Metzler et al. (Nature Structural Biol. 1997; 4:527-531) show that any of a variety of single amino acid changes can alter or abolish the ability of CTLA4 to interact with its ligands CD80 and CD86 (e.g., summarized in Table 2).

Given the absence of sufficient number of working examples of species that share the disclosed functional activities and have less than 100% identity over the full length of the sequence set forth in SEQ ID NO:2, the skilled artisan would not reasonably expect a polypeptide having anything less than *100% identity* over *the full length* of this sequence to share the same function as the polypeptide of SEQ ID NO:2. The limitation of "having an activity of the polypeptide set forth in SEQ ID NO: 2" is not seen as providing a requisite functional activity for the nucleic acid encoding the polypeptide both because, as noted supra, the term is ambiguous; and because even if the polypeptide is limited in binding to the PD-1 receptor or inhibiting anti-CD3 mediated T-cell proliferation, the instant specification does not provide sufficient nexus between those activities and the claimed nucleic acids encoding the claimed polypeptide to place applicant in possession of the claimed genus.

Neither is the term "antigenic" (claim 2(c)) seen as sufficiently limiting since antigenic peptides may be as small as 6-15 shared amino acid residues (e.g., Lerner: Nature 1982; 299:592-596, see page 595-596) and places insufficient limitations on the function of the protein containing the polypeptide sequence.

Thus the recitation of percent identity language, in the absence of *a testable function* and limitations regarding the *sequence length* over which the percent identity is required; does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

(B) "Hybridization"

Similarly, the fact that two nucleic acid sequences will hybridize under at least moderately stringent conditions (claims 1(d), 2(e), and 3(g)) does not in and of itself require that the two sequences share any functional activity. Thus the same observations apply to the recitation of "a nucleic acid that hybridizes under moderately stringent hybridization conditions" as were noted above with respect to "percent identity" language. Further, it was well known in the art at the time the invention was made that hybridization could occur between two sequence based upon short stretches of 100% identity. Thus a great deal of sequence variability *with respect to the full-length nucleic acid* is possible. Finally, hybridization under conditions other than high stringency would be expected to permit a great deal of variation between the two hybridizing sequences, making the possession of sequences that would share the same function even more difficult to achieve.

Thus as for the recitation of percent identity, hybridization language in the absence of *a testable function* and limitations regarding both the *hybridization conditions* and the *sequence length* over which the hybridization takes place; does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

(C) "Allelic variants or splice variants"

The term "allelic variants" encompasses "one of several possible naturally occurring alternate forms of a gene occupying a given locus on a chromosome of an organism or a population of organisms," as disclosed in the specification as-filed on page10, lines 20 – 23. Similarly, a "splice variant" is a reference to "a nucleic acid molecule, usually RNA, which is generated by alternative processing of intron sequences in an RNA transcript of B7-L polypeptide" (page 10 lines 23 – 26). Applicant has not provided sufficient biochemical information (e.g. nucleic acid sequences, etc.) that distinctly identifies the allelic variants or splice variants of SEQ ID NO:1, (claim 2(b)), other than those set forth in SEQ ID NO:1 and ATCC Deposit No. PTA 2481.

It is not sufficient to define a specificity by its principal biological activity or structure, e.g. for allelic variants or splice variants of SEQ ID NO:2, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property. The specification appears to provide insufficient data on the existence of allelic variants or splice variants of SEQ ID NO:2.

Thus, applicant has not provided sufficient guidance to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed protein in manner reasonably correlated with the scope of the claims broadly including any number of allelic variants or splice variants of SEQ ID NO:2. The scope of the claims must bear a reasonable correlation with the scope of the written description. The specification does not provide for sufficient written description for allelic variants or splice variants of SEQ ID NO:2 other than that defined by SEQ ID NO:2.

(D) "modifications"

The instant claim language encompasses modifications of SEQ ID NO:2, such as amino acid substitutions, deletions, and insertions (claim 3). Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, Burgess et al (J Cell Biol. 111:2129-2138, 1990) show that a conservative replacement of a single "lysine" reside at position 118 of acidic fibroblast growth factor by "glutamic acid" led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. Similarly, Lazar et al. (Mol Cell Biol. 8:1247-1252, 1988) teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagines did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. Also, as noted supra, Metzler et al. (Nature Structural Biol. 1997; 4:527-531) show that any of a variety of single amino acid changes can alter or abolish the ability of CTLA4 to interact with its ligands CD80 and CD86 (e.g., summarized in Table 2). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein.

Furthermore, the specification fails to teach what deletions, truncations, substitutions and mutations of the disclosed sequence can be tolerated that will allow the protein to function as claimed. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with reasonable expectation of success are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or no substitutions. Residues that are directly involved in protein functions such as binding will certainly be among the most conserved (Bowie et al. Science, 247:1306-1310, 1990, p 1306, col. 2).

Thus the recitation of a range of possible protein sequence modifications, in the absence of guidance as to the specific nature of modifications resulting in a functional polypeptide, does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

(E) subsequences and complementary sequences.

The instant claim language appears to encompass subsequences. For example, claim 1(d) recites an isolated nucleic acid molecule that hybridizes to the complement of SEQ ID NO:1. Even under high stringency conditions, molecules shorter than the specified sequence are expected to meet this limitation. Further, claims 2(c) – 2(f) and 3(d) – 3(h) specifically read on regions, fragments, and truncations of SEQ ID NO:1.

However, the specification does not appear to have provided sufficient guidance as to which subsequences of SEQ ID NO:2 would share the activity of binding to PD-1 or inhibiting anti-CD3 mediated T-cell proliferation. Neither does the specification appear to have provided any working examples of any functional subsequences. Thus the inventor(s), at the time the application was filed, do not have possession of the claimed invention, other than the isolated nucleic acid molecules of SEQ ID NO:1, the nucleotide sequence of DNA insert in ATCC deposit No. PTA 2481, and a nucleotide sequence encoding the polypeptide as set forth in SEQ ID NO:2.

The recitation of "a nucleotide sequence complementary to the nucleotide sequence" in claims 1(e), 2(f), and 3(h) without further limitation that the complementarity is over the full length of the sequence, reads on subsequences and is subject to rejection on the grounds specified above.

The term "comprising" in claims 1 – 3 is open ended and extends the nucleic acid molecule to include additional non-disclosed sequences on either or both sides of the disclosed region. As the term "comprising" is applied to sequences other than full length B7-L sequences, such as regions, fragments, of hybridizing or complementary nucleic acid molecules, there does not appear to be sufficient description in the specification as filed to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

A person of skill in the art would not know which sequences are essential, which sequences are non-essential, and what particular sequence lengths identify essential sequences. There is insufficient description to direct a person of skill in the art to select particular sequences or sequence lengths as essential for binding to PD-1 or inhibiting anti-CD3 mediated T-cell proliferation. Without detailed description as to which nucleic acid sequences are essential to the function of the encoded polypeptide, a person of skill in the art would not be in possession of a sufficient number of species that would support the plethora of nucleic acid sequences encompassed by the instant claims that would share the ability to bind to PD-1 or inhibit anti-CD3 mediated T-cell proliferation of the encoded polypeptide of SEQ ID NO:2, other than the nucleic acid of SEQ ID NO:1 the nucleotide sequence of DNA insert in ATCC deposit No. PTA 2481, and a nucleotide sequence encoding the polypeptide as set forth in SEQ ID NO:2.

Thus the written description of the invention fails to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the fragments, regions, and other subsequences of B7-L of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

The specification therefore fails to provide an adequate written description of the above noted claim limitations. As noted supra, the skilled artisan would not reasonably expect a polypeptide having anything less than *100% identity* over *the full length* of SEQ ID NO:2 to share the same function as B7-L. The limitation of "having an activity" is not seen as providing a requisite written description, because even if the activity is specified as binding to the PD-1 receptor and/or inhibiting anti-CD3 mediated T-cell proliferation, the specific sequences necessary for these properties are still unknown. Even though the specification describes how to test the nucleic acid sequences to determine whether they encode functional polypeptides, it does not set forth any procedure that will necessarily lead to discovery of such sequences, nor does it even identify any particular example of such variant sequences.

Applicant is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Alternatively, limiting the scope of the claims in this Application to that of claims 1(a) – 1(c) would obviate this rejection.

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

16. Claims 1 – 8, 10, 11, and 43 are rejected under 35 U.S.C. 102(e) as being anticipated by Mikesell et al. (US 2002/0095024, see entire document), as evidenced by the attached sequence alignment.

Mikesell et al. teach the nucleic acid sequence SEQ ID NO:14 encoding the BSL3 polypeptide SEQ ID NO:15 (see Claim 1; Paragraph 0048; and Fig. 5). The nucleic acid sequence of SEQ ID NO:14 of Mikesell et al. is 100% identical to nucleotides 19 – 1209 of SEQ ID NO:1 of the instant application, and the amino acid sequence of SEQ ID NO:15 of Mikesell et al. is 100% identical to SEQ ID NO:2 of the instant application, as evidenced by the attached alignment.

Mikesell et al. also teach (see Summary of the Invention: B7-related Nucleic Acids, paragraphs 0047 – 0070; B7-related Nucleic Acid Expression Vectors, paragraphs 0071 – 0086; B7-related Polypeptides, paragraphs 0087 – 0101, and Claims, page 42 – 44):

> Nucleic acid molecules that hybridize to BSL3 under moderate or high stringency conditions (0062);

Nucleic acid molecules comprising a sequence which is complementary to BSL3 (see claim 7);

Isolated nucleic acids sharing at least 60% identity with a polynucleotide sequence of BSL3 (0051, see also claim 3e), including as determined by algorithms such as BLASTN2 (0053);

Naturally occurring polymorphisms and splice variants of BSL3 (0059 and 0056);

Fragments of BSL3 of at least 15 nucleotides (0069, see also claim 6e);

Nucleotide sequences and fragments encoding functionally equivalent B7-related factors (0050);

Modifications of BSL3 nucleotide sequence to introduce amino acid substitutions, deletions, or insertions into the encoded polypeptide (0067, 0092 – 0098);

Expression vectors comprising BSL3, including those containing heterologous promoters (0072, 0073, see also claim 10);

Host cells (prokaryotic and eukaryotic) for expression of recombinant BSL3 (0073, see also claim 13);

Methods for producing BSL3 polypeptide by expression in host cells (0079, 0310);

Pharmaceutical compositions comprising BSL3 nucleic acid molecules (0161, see also claim 21);

Activity of BSL3 in modulating the activation of immune or inflammatory response cells, such as T-cells (0002).

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the nucleic acid molecule SEQ ID NO:14 and modifications and fragments thereof of Mikesell at al.

In particular, because Mikesell et al. teach a nucleic acid molecule identical in sequence to SEQ ID NO:1 of the instant application, it would necessarily encode a polypeptide which has an activity of the polypeptide set forth in SEQ ID NO:2 of the instant claimed invention.

The reference teachings thus anticipate the instant claimed invention.

17. Claims 1 – 8, 10, 11, 43 – 45, 57, and 58 are rejected under 35 U.S.C. 102(e) as being anticipated by Coyle et al. (U.S. Pat. No. 6,630,575, see entire document), as evidenced by the attached alignment.

Coyle et al. teach an isolated nucleic acid molecule (SEQ ID NO:1), which encodes a polypeptide, B7-H2 long (B7-H2l, SEQ ID NO:2) (see Claim 1; Fig. 1; column 5 lines 50 – 55; column 19 line 52 – column 20 line 21). The nucleic acid sequence of SEQ ID NO:1 is 100% identical to nucleotides 19 – 1209 of SEQ ID NO:1 of the instant application, and the amino acid sequence of SEQ ID NO:2 is 100% identical over its entire length to SEQ ID NO:2 of the instant application, as evidenced by the attached alignment.

Coyle et al. also teach the following (see Detailed Description of the Invention, columns 10 – 58):

Nucleic acid molecules that hybridize to B7-H2l under stringent conditions (col. 24 – 24);

Nucleic acid molecules that are complementary to B7-H2l (col. 20 lines 5 - 10);

Variant B7-like nucleotide sequences which encode proteins that have an amino acid sequence having at least about 70% identity to the amino acid sequence of B7-H2l (column 21 lines 20 – 25), and determination of percent identity using mathematical algorithms, such as NBLAST and XBLAST (column 16 lines 22 – 55);

Naturally occurring allelic variants of B7-H2l (column 21 lines 4 – 15);

Fragments of the nucleotide sequence of B7-H2l of at least about 15 nucleotides (column 20, lines 34 – 45);

Fragments of nucleotide sequence that encode a biologically active portion of B7-H2l of at least about 20 contiguous amino acids (column 20, lines 57 – 66);

Modifications of B7-H2l nucleotide sequence to introduce amino acid substitutions, deletions, or insertions into the encoded polypeptide (column 22 lines 1 – 13);

Recombinant expression vectors and host cells comprising B7-H2l (columns 32 – 35);

Host cells which are eukaryotic or prokaryotic cells (column 33);

Expression vectors comprising heterologous promoters (column 34 lines 4 – 25);

Method for producing B7-H2l protein using the host cells of the invention (column 35 lines 7 – 19);

B7-H2l nucleic acid molecules incorporated into pharmaceutical compositions (column 37 lines 11 – 29);

B7-H2l nucleic acid incorporated into a viral vector (column 32 lines 25 – 45);

B7-H2l nucleic acid molecules inserted into gene therapy vectors, such as retroviral vectors, and further incorporated into a pharmaceutical preparation (column 40, lines 51 – 64);

A two-dimensional array having a plurality of nucleic acid probes and capable of capturing B7-like nucleic acids (column 49, lines 46 – 65; see also column 50 lines 12 – 24 and column 52 lines 47 – 67);

An activity of B7-H2l in modulating immune responses (column 4, lines 36 – 58).

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the isolated nucleic acid molecule SEQ ID NO:1 and modifications and fragments thereof taught by Coyle et al.

In particular, because Coyle et al. teach a nucleic acid molecule identical in sequence to SEQ ID NO:1 of the instant application, it would necessarily encode a polypeptide which has an activity of the polypeptide set forth in SEQ ID NO:2 of the instant claimed invention.

The reference teachings thus anticipate the instant claimed invention.

18. Claims 1 – 8, 10, 11, and 43 – 45 are rejected under 35 U.S.C. 102(e) as being anticipated by Freeman et al. (US 2002/0110836, see entire document), as evidenced by the attached alignment.

Freeman et al. teach an isolated nucleic acid molecule (SEQ ID NO:1), which encodes a polypeptide, PD-L2 (SEQ ID NO:2) (see Fig. 1 and paragraph 0060). The nucleic acid sequence of SEQ ID NO:1 is 100% identical to nucleotides 19 – 982 of SEQ ID NO:1, and the amino acid sequence of SEQ ID NO:2 is 100% identical over its entire length to SEQ ID NO:2 of the instant application of the instant application, as evidenced by the attached alignment. Freeman et al. teach that interaction of PD-L2 with PD-1 transmits a negative signal to immune cells, downregulating immune responses (paragraph 0011).

Freeman et al. also teach the following (see Detailed Description of the Invention, paragraphs 0076 – 0377):

Nucleic acid molecules that hybridize to PD-L2 under stringent conditions (0148 - 0151);

Nucleic acid molecules that are complementary to PD-L2 (0135);

Nucleic acid molecules which encode polypeptides that have an amino acid sequence having at least 71% identity to the amino acid sequence of PD-L2 (0153), and determination of percent identity using mathematical algorithms, such as the GAP program in the GCG software package (0177);

Natural allelic variants and homologues of PD-L2 (0147);

Fragments of the nucleotide sequence of PD-L2 of at least about 12 or 15 nucleotides (0137);

Nucleic acid fragments encoding a biologically active portion of a PD-L2 polypeptide (0140)

Modifications of PD-L2 nucleotide sequence to introduce amino acid substitutions, deletions, or insertions into the encoded polypeptide (0154);

Recombinant expression vectors and host cells comprising PD-L2 (0206 – 228);

Host cells which are eukaryotic or prokaryotic cells (0220);

Expression vectors comprising heterologous promoters (0217);

Method for producing PD-L2 protein using the host cells of the invention (0223);

PD-L2 nucleic acid molecules incorporated into pharmaceutical compositions (0230);

PD-L2 nucleic acid incorporated into a viral vector (0215);

PD-L2 nucleic acid molecules inserted into gene therapy vectors, such as retroviral vectors, and further incorporated into a pharmaceutical preparation (0249);

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the isolated nucleic acid molecule SEQ ID NO:1 and modifications and fragments thereof taught by Freeman et al.

In particular, because Freeman et al. teach a nucleic acid molecule identical in sequence to SEQ ID NO:1 of the instant application, it would necessarily encode a polypeptide which has an activity of the polypeptide set forth in SEQ ID NO:2 of the instant claimed invention.

The reference teachings thus anticipate the instant claimed invention.

19. Claims 1 – 8, 10, 11, and 45 are rejected under 35 U.S.C. 102(e) as being anticipated by Fiscella et al. (US 2003/0208058, see entire document), as evidenced by the attached alignment.

Fiscella et al. teach an isolated nucleic acid molecule (SEQ ID NO:3), which encodes a polypeptide B7-H7 (SEQ ID NO:15) (see Fig. 3 and paragraph 0031). The nucleic acid sequence of SEQ ID NO:1 is 100% identical to nucleotides 19 – 1209 of SEQ ID NO:1, and the amino acid sequence of SEQ ID NO:2 is 100% identical over its entire length to SEQ ID NO:2 of the instant application of the instant application, as evidenced by the attached alignment. Ficsella et al. teach that B7-H7 protein inhibits B-cell proliferation (see Fig. 15 and Example 21, paragraphs 1248 – 1250).

Fiscella et al. also teach the following (see Features of Protein Encoded by Gene No: 2, paragraphs 0093 – 0129):

Nucleic acid molecules that hybridize to B7-H7 under stringent conditions (0096);

Nucleic acid molecules that are complementary to B7-H7 (0096);

Nucleic acid molecules which encode polypeptides that have an amino acid sequence having at least 80% identity to the amino acid sequence of B7-H7 (0096);

Fragments of the nucleotide sequence of B7-H7 of at least about 15 nucleotides (0108);

Nucleic acid fragments encoding truncations of a B7-H7 polypeptide (0109 - 0115)

Modifications of B7-H7 nucleotide sequence to introduce amino acid substitutions into the encoded polypeptide (0337);

Recombinant expression vectors and host cells comprising B7-H7 (0342 – 0356);

Host cells which are eukaryotic or prokaryotic cells (0346);

Expression vectors comprising heterologous promoters (0345);

Method for producing B7-H7 protein using the host cells of the invention (0352);

B7-H7 nucleic acid incorporated into a viral vector (0343);

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the isolated nucleic acid molecule SEQ ID NO:3 and modifications and fragments thereof taught by Fiscella et al.

In particular, because Fiscella et al. teach a nucleic acid molecule identical in sequence to SEQ ID NO:1 of the instant application, it would necessarily encode a polypeptide which has an activity of the polypeptide set forth in SEQ ID NO:2 of the instant claimed invention.

In claim 11 of the instant invention, the recitation of the process limitation is not seen as further limiting the claims as it is presumed equivalent products cam be obtained by multiple routes.

The reference teachings thus anticipate the instant claimed invention.

20. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

21. Claims 44 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mikesell et al. (US 2002/0095024) and/or Fiscella et al. (US 2003/0208058), each in view of Nabel et al. (US Pat. No. 5,328,470).

The claims are drawn to a viral vector comprising B7-L nucleic acid molecules and a composition comprising such viral vector and a pharmaceutically acceptable agent.

Mikesell et al. and Fiscella et al. have been discussed supra and teach nucleic acid molecules identical in sequence to B7-L of the instant application. Mikesell et al. and Fiscella et al. also teach that the proteins encoded by these nucleic acid molecules are involved regulation of immune cells.

Mikesell et al. and Fiscella et al. do not explicitly teach these nucleic acid molecules as part of a viral vector in a pharmaceutically acceptable formulation.

Nabel et al. (see entire document) teach the use of nucleic acid molecules which encode immune stimulants and/or immune and growth stimulants/inhibitors (column 13 line 66 – column 14 line 19), incorporated into retroviral vectors, herpes virus, adenovirus, and other viral vectors (column 8 lines 47 - 53), and further instilled in a pharmaceutically acceptable media (e.g. a polycationic substance which is "physiologically suitable," see column 8 lines 8 – 19). Nabel et al. teach these compositions as they relate to a method for modulating the immune system of an animal by the in vivo introduction of recombinant genes (column 1 lines 15 – 20), with the goal of treating diseases (column 4 lines 43 – 47).

Given the teachings of Mikesell et al. and Fiscella et al. that molecules identical to B7-L of the instant application are involved regulation of immune cells, and the teachings of Nabel et al. who incorporate nucleic acid molecules encoding immune stimulants or inhibitors into viral vectors and further into pharmaceutically acceptable compositions, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of Nabel et al. to those of Mikesell et al. and Fiscella et al. to obtain a claimed viral vector comprising a B7-L nucleic acid molecule or a composition comprising such vector and a pharmaceutically acceptable formulating agent.

Furthermore, the ordinary artisan would have been motivated to utilize B7-L nucleic acids as part of a viral vector and further as part of a pharmaceutically acceptable composition, as taught by Nabel et al., with a reasonable expectation that such formulation will be useful for modulating the immune system of an animal with the goal of treating diseases, as also taught by Nabel (see column 1 lines 15 – 20 and column 4 lines 43 – 47). Given that Mikesell et al. and Fiscella et al. teach that molecules identical to B7-L are involved in immune cell regulation, the ordinary artisan would have recognized that such molecules could be employed for modulating the immune system of an animal by incorporating then into a viral vector and further into a composition comprising such vector and a pharmaceutically acceptable formulating agent, as claimed in the instant application.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

22. Claims 57 and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mikesell et al. (US 2002/0095024) and/or Freeman et al. (US 2002/0110836) and/or Fiscella et al. (US 2003/0208058), each in view of Ollila et al. (Biocem. Biophys. Res. Comm., (1998) 249:475).

The claims are drawn to B7-L nucleic acid molecules attached to solid support, or an array of nucleic acid molecules comprising B7-L nucleic acid molecules.

Mikesell et al., Freeman et al., and Fiscella et al. have been discussed supra and teach nucleic acid molecules identical in sequence to B7-L of the instant application. Mikesell et al., Freeman et al., and Fiscella et al. also teach that the proteins encoded by these nucleic acid molecules are involved in signaling and regulation of T cells.

Mikesell et al., Freeman et al., and Fiscella et al. do not explicitly teach attaching these nucleic acid molecules to solid support or using them as part of a microarray.

Ollila et al. (see entire document) teach the use of DNA microarray technology for the analysis of stimulation of B and T cells. Ollila et al. also teach that placing nucleic acid molecules that recognize T cell signaling and regulatory molecules, such as CD40L (see page 478 and table 2), on a microarray is useful to detect changes in gene expression during immune cell signaling and "to increase our knowledge about mechanisms and proteins of the leukocytes which are functional during stimulation, proliferation and differentiation" (Page 479).

Given the teachings of Mikesell et al., Freeman et al., and Fiscella et al. that molecules identical to B7-L of the instant application are involved in signaling and regulation of T cells, and the teachings of Ollila et al. that placing nucleic acid molecules that recognize T cell signaling and regulatory molecules on a microarray is useful to increase our understanding of T cell regulation, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of Ollila et al. to those of Mikesell et al., Freeman et al., and Fiscella et al. to obtain a claimed array of nucleic acid molecule comprising B7-L molecules. Given the teachings of the references, the ordinary artisan would have had a reasonable expectation of success in producing an array comprising B7-L nucleic acid molecules.

Furthermore, the ordinary artisan would have been motivated to utilize B7-L nucleic acids as part of an array as taught by Ollila et al. with a reasonable expectation that such an array will be useful for detecting changes in gene expression during immune cell signaling. Given that Mikesell et al., Freeman et al., and Fiscella et al. teach that molecules identical to B7-L are involved in T cell signaling, the ordinary artisan would have recognized that such molecules could be employed for detection of changes in gene expression during T cell activation by placing them on a solid support and using them as part of an array, as claimed in the instant application.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

23. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILIA OUSPENSKI whose telephone number is 571-272-2920. The examiner can normally be reached on Monday-Friday 9 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

ILIA OUSPENSKI
Examiner
Art Unit 1644

May 21, 2004

PHILLIP GAMBEL, PH.D
PRIMARY EXAMINER
TECH CENTER 1600
5/24/04